Review

Discovery Medicine 2025; 37(200): 1787–1799
https://doi.org/10.24976/Discov.Med.202537200.155

The Intestinal Microbiota: An Environmental Effector for the Endocannabinoid System and Medicinal Cannabis in Inflammatory Bowel Disease

Luis Vitetta[1,*], Debbie Oldfield[2,3], Michael Thomsen[4]

[1]Faculty of Medicine and Health, The University of Sydney, 2050 Camperdown, NSW, Australia
[2]National Institute of Integrative Medicine, 3122 Melbourne, VIC, Australia
[3]Health House, 6000 Perth, WA, Australia
[4]National Centre for Naturopathic Medicine, Southern Cross University, 2480 East Lismore, NSW, Australia
*Correspondence: luis.vitetta@sydney.edu.au (Luis Vitetta)
Submitted: 30 April 2025 Revised: 30 May 2025 Accepted: 25 June 2025 Published: 20 September 2025

Inflammatory bowel disease (IBD) is a condition that is subject to genetic and environmental factors, characterized by multifaceted proinflammatory responses, which consequently can affect both hematological and non-hematological structures in the intestines. Gut microbiota dysbiosis is an environmental trigger posited to dysregulate the local immune system, initiating a complex interplay with a genetic predisposition to maintain the condition. Medicinal cannabis investigations on their anti-inflammatory characteristics have not been consistent with reports from laboratory studies with murine models. Although oral administration of medicinal cannabis, single molecules, or as mixed extracts from the flowering plant has been deemed safe, human clinical studies have not provided objective anti-inflammatory efficacy for conditions such as IBD. Anti-inflammatory efficacy was not observed for either ulcerative colitis (UC) or Crohn's disease (CD) with either Δ9-Tetrahydrocannabinol + Cannabidiol (Δ9-THC + CBD) or CBD alone, while improving the quality of life (QoL) of patients diagnosed with IBD. Mechanistically, what the current research shows is that the endocannabinoid system (ECS) tone in the gut is subject to intestinal microbiota homeostasis. Intestinal dysbiosis, as described for IBD, is posited to disturb the tone of the ECS, thereby disrupting the effects that medicinal cannabis may have in the treatment of gut inflammation. Conditions of IBD are linked with gut and vermiform appendix microbiota dysbiosis, characteristics in the colon that may destabilize the tone of the ECS and lead to medicinal cannabis failures to achieve clinically objective anti-inflammatory effects. The aim of this review is to investigate the link between the intestinal microbiota, the ECS and IBD. The quick, natural fix that medicinal cannabis appears to provide to manage the underlying IBD disease may not be suitable for all patients diagnosed with UC or CD.

Keywords: intestinal microbiota; inflammatory bowel disease; Crohn's disease; ulcerative colitis; medicinal cannabis; endocannabinoid system; inflammation; C-Reactive Protein

Introduction

A recent global report that reviewed the epidemiology of inflammatory bowel diseases (IBD) with real-world data derived from 522 population-based studies reported on the incidence (n = 463) and/or prevalence (n = 243) of Crohn's disease (CD) and/or ulcerative colitis (UC), in an all-inclusive study from 82 countries bridging the years from 1920–2024 [1,2]. The epidemiological trends reported show the incidence and prevalence of IBD in the 20th century followed distinct geographical and temporal patterns [2]. The authors report that IBD was considered a disease of industrialized regions covering North America, Europe and Oceania. In the 21st century, the incidence of IBD has increased in newly industrialized and emerging regions such as Africa, Asia and Latin America, while the prevalence in early industrialized regions has continued to steadily increase. In addition, Hracs and colleagues [1] have noted that changes in the incidence and prevalence of IBD denote the evolution of disease across four epidemiologic stages. That is stage 1 outlines the emergence of the disease that is characterized by a low incidence and prevalence; whereas stage 2 incorporates an acceleration of the incidence that presents a rapid and pronounced increase in incidence with a low prevalence; and stage 3 compounding the prevalence of the disease, with a decelerating incidence, as it levels out or decreases with a concomitant steady increase in IBD prevalence [1]. An equilibrium in IBD prevalence is a fourth stage posited where the prevalence slope plateaus due largely to the ageing population's demographic shifts [1]. Accordingly, a recent opinion report has investigated the implications for health that changes related to modern lifestyle are reflected in the composition of the gut microbiome of different populations [3]. The accelerated

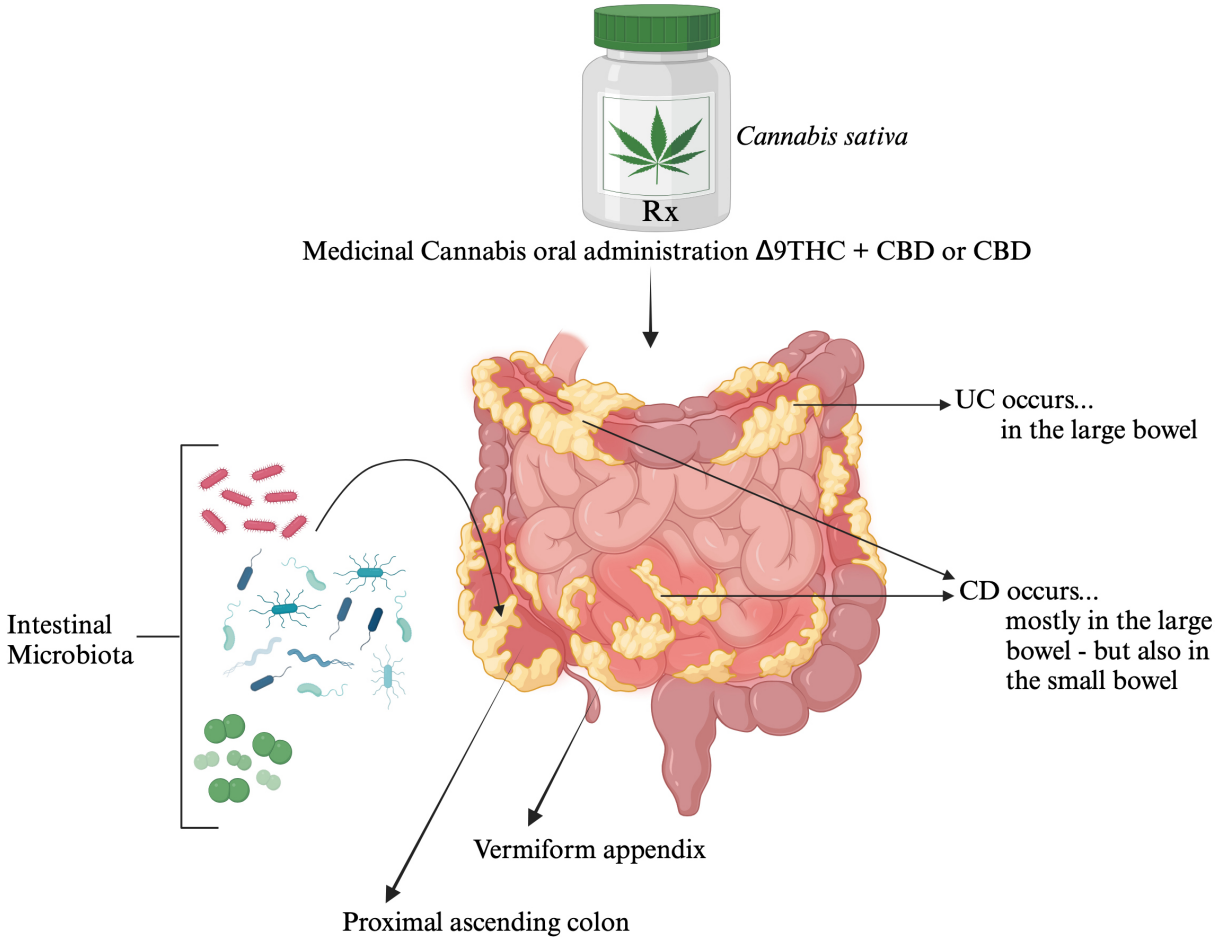

Fig. 1. Diagrammatic representation of orally administered medicinal cannabis prescribed for inflammatory bowel diseases in humans. [Created in BioRender]. Δ9THC, Δ9-Tetrahydrocannabinol; CBD, Cannabidiol; UC, ulcerative colitis; CD, Crohn's disease.

rate of industrialization may be an important factor that has been linked to the increased risk of IBD in countries like China [4].

The consensus on the aetiology of IBD is reported to be linked with the interaction of encouraging factors from the environment, immunity, physiological, psychological and the gut microbiota that may drive genetic dispositions [5]. Specifically, IBD is a chronic, nonspecific, relapsing intestinal inflammatory disease grouped into UC and CD. Patients usually report developing gut symptoms such as abdominal pain, diarrhea, dyspepsia, and blood in the stool, and some patients also report peripheral manifestations. Patients can also experience a common digestive condition, irritable bowel syndrome (IBS), that presents with stomach complaints, abdominal pain, bloating, and either diarrhea or constipation, which can very much exacerbate diagnoses of chronic illnesses such as UC or CD [5,6]. Medicinal cannabis has been administered as a treatment option to reduce inflammatory sequelae in IBD (Fig. 1) [7].

Assessment of neuro-visceral integration, core microbiota analysis, and immune modulation has been posited to hold promise for identifying novel diagnostic and treatment modalities for inflammatory gut conditions [8]. The gut microbiota ecosystem supports a microbiota-host cross-talk with the intestinal bacteria signalling to extraintestinal organs [9]. Conforming with these characteristics is the emerging clinical and laboratory research that continues to teach that there is a complex bidirectional interaction between the oral use of medicinal cannabis and the intestinal microbiota [10]. The cannabis molecules identified in the *Cannabis sativa* Linn. plant, encompassing delta-9-tetrahydrocannabinol (D9-THC), the major psychophytoconstituent molecule, delta-8-tetrahydrocannabinol (D8-THC), cannabidiol (CBD), cannabinol (CBN) and cannabigerol (CBG), have been considered and hypothesized to have clinical relevance in IBD [11].

It is widely accepted that the endocannabinoid system (ECS) contributes to gut physiological equilibrium [12]. The capacity of the ECS to efficiently temper the tone of inflammatory responses and permeability in the gut establishes the competence of the ECS to preserve gastrointestinal functions [12]. Clinical studies with IBD patients have reported contentious health benefits from the use of cannabis in IBD, through a reduction of IBD-inflammation

and a decreased request for pharmaceutical medications [13]. Notwithstanding, adverse changes in the equilibrium of the ECS could predispose patients to pathologic IBD disorders [13].

The Tone of the Intestinal ECS

The ECS is a system that encompasses endocannabinoids (i.e., anandamide, 2-arachidonoylglycerol) with associated synthesis and degradation enzyme systems and type 1 (CB_1) and type 2 (CB_2) receptors [14]. Mechanistically, the endocannabinoidome [15,16] is linked to the intestinal microbiome. This association is reported to provide mutual interactions that control intestinal homeostasis, energy metabolism, and neuroinflammatory responses during physiological conditions [16]. In addition to this complex nature of intestinal ECS tone, the varying affinities of cannabis molecules for ECS receptors further complicate the picture. For example, THC exhibits high-affinity binding to CB_1 receptors, while CBD has low-affinity binding for both CB_1 and CB_2 receptors. Although THC has a high affinity for CB_1 and can mediate abuse-related and reinforcing effects, CBD has a complex pharmacology that is emphasized by binding and acting on multiple types of receptors (e.g., adenosine receptors, adenosine receptors, Transient Receptor Potential Vanilloid 1 [TRPV1], G-protein-coupled receptor 55 [GPR55], 5-Hydroxytryptamine Receptor 1A [5-HT1A]) [17,18]. CB_1 and CB_2 receptors are extensively expressed in the gut [19]. The activity of CB_1 receptors is present in the myenteric and submucosal plexus. In addition, CB_1 receptors are also expressed in the enteric nervous system, specifically cholinergic neurons and afferent vagal neurons [19]. Whereas CB_2 receptors are expressed in immune cells and epithelial cells of the mucosa.

There is compelling evidence that the intestinal ECS is an important participant in regulating mood disorders such as anxiety and depression [19]. Linked to this is also convincing research that has demonstrated that reduced levels of intestinal microbiota species are a key factor in the progression of mood disorders [18]. Changes that express the tone of the intestinal ECS underpin a ubiquitous signalling system that contributes to gut homeostasis [20]. There is an extensive crosstalk in the intestines between the ECS and the microbiota that features numerous gut functions such as hormonal secretion, nutrient absorption, intestinal permeability and motility, as well as local and possibly systemic immune responses [19]. Reports posit that the gut microbiota may influence the regulation of anxiety, memory, the stress response, and driven behaviours that can affect overall social functioning [21]. Consideration of the workings of the intestinal ECS system remains limited when linked to the gut microbiota and the repetitive use of cannabis as self-medication or medical prescriptions to treat ailments [22]. Prescriptions for medicinal cannabis are usually specified for the treatment of mood disorders such as anxiety and depression [23]. Mood disorders have a significant association with intestinal dysbiosis [24]. This effect can be compounded with the oral use of cannabis products containing THC [25]. It is also known that cannabis can disrupt the tone of the ECS, as evidenced by the reported daily use of cannabis [26]. Specifically, neuroadaptations in the ECS can develop with down-regulation of CB_1 receptors, which has been shown that with abstinence from cannabis use, this effect can be reversed within days of cessation of use [27]. It is possible to posit that the ineffective oral use of medicinal cannabis illustrates the complexity that exists between the intestinal ECS system [18] and its proximity to the body of bacteria that inhabit the intestines. The intricate tone of ECS can be affected by the metabolic activities of intestinal bacterial infections [28]. Notwithstanding, Osman and colleagues [28] have reported that the ECS has been identified as a promising target in the treatment of IBD with medicinal cannabis. Consistent with this view, experimental studies have shown that the ECS system and the elaborated endocannabinoids are directly sensed by bacteria and can modulate bacterial function [29].

Yet, clinical studies have not supported this contention (Table 1, Ref. [30–37]).

IBD and Medicinal Cannabis

Medicinal cannabis is often prescribed to manage inflammatory symptoms of abdominal pain and gut inflammation and gut disruptions, such as frequency, suggesting that it may be a useful treatment for IBD [38]. Table 1 presents clinical studies that show that medicinal cannabis has limited efficacy in the treatment of intestinal inflammation and more importantly, in the control of inflammation in IBD. Yet there are only a limited number of clinical studies that have demonstrated that medicinal cannabis was not significantly better than a placebo in improving inflammation with either CBD or THC extracts. Investigations that have administered cannabis extracts through the oral or respiratory tract, aiming to reduce gut inflammation by improving blood C-Reactive Protein (CRP) levels at 8 and 12 weeks, have shown no difference between cannabis extracts tested and placebo (Table 1). Notwithstanding those clinical studies reported significant improvements in subjective measures as reported with quality of life (QoL) and in disease activity with the Lichtiger Disease Activity Index (LDAI) [30], inflammatory bowel disease questionnaire (IBDQ) score, and the physician global assessment of illness severity (PGAS) [31] score, indices that are not IBD remission markers but rather disease activity measures. Whereas Naftali and colleagues [32,33] have reported on a possible remission of the disease with the Crohn's disease Activity Index (CDAI), yet no effect was reported on an objective inflammatory marker (e.g., blood C-Reactive Protein) (Table 1).

Table 1. Placebo-controlled clinical studies investigating the effect of inhaled or orally administered medicinal cannabis formulations on IBD.

Cannabis source [n = participants] (reference)	Study type and condition	Dose administered	IBD
Human Clinical Studies			
CBD-rich oil Assessing the effect on the induction of remission in CD. (56) [32]	DBPCRCT Single center —patients with CD	Orally administered —0.05 mL containing 8 mg CBD and 2 mg THC —placebo olive oil and Chlorophyll Dose 1 drop b.i.d. —8 weeks	—CBD is safe and well tolerated. —CBD-rich cannabis treatment. Induced ↑significant improvement in clinical and QoL. —LDAI improved in test v placebo ($p = 0.006$). —inflammatory parameters or endoscopic scores ($p > 0.05$) —CRP ($p > 0.05$) between groups.
THC Source dried flowers of genetically identical plants of *Cannabis sativa* var. Indica "Erez" (courtesy of Tikun-Olam Ltd., Tel Aviv, Israel) (32 UC) [34]	DBPCRCT —patients with UC	Smoking administered —dose: 80 mg 16% THC —additional content: 0.5% CBG 0.1% CBD traces <0.1% CBC | CBDV | Δ8THC —8 weeks	—Short-term treatment with THC-rich cannabis induced clinical remission. ↑ QoL in mild to moderate active UC. —LDAI improved in test v placebo ($p = 0001$). —Clinical response 10/11 vs 4/10 in placebo group ($p = 0.028$). —Complete remission in 5/11. —Beneficial clinical effects were not associated with significant anti-inflammatory improvement. —CRP ($p > 0.05$) between groups.
THC Source dried flowers, genetically identical plants of *Cannabis sativa* var. Indica "Erez" (courtesy of Tikun-Olam Ltd., Tel Aviv, Israel) (13 CD | 9 UC) test [17 CD | 10 UC] controls [30]	PRCT —patients with DC and UC	Smoking administered —0.5 g dried cannabis flowers equivalent to 11.5 mg of THC flowers treated with *Saccharomyces cerevisiae* var. 18 final product <0.4% THC undetectable amounts of all other cannabinoids, including CBD —8 weeks	levels of eCBs remained unaltered. —↓ significant PEA, AEA, and AA levels in the UC placebo only. —↓ bowel frequency negatively related to levels of circulating AEA | OEA. —↑ QoL is positively correlated to 2-AG —CRP not measured. —improved LDAI and QoL scores test over placebo ($p < 0.05$). —CRP not reported.

Table 1. Continued.

Cannabis source [n = participants] (reference)	Study type and condition	Dose administered	IBD
CBD-rich botanical extract [37] (39 completed study) [31]	DBPCRCT parallel allocation —Patients with mild to moderate UC	Oral administration —50 mg CBD-rich extract versus placebo (1:1) b.i.d. —12 weeks	The primary endpoint was negative —End of treatment remission rates were similar for CBD-rich botanicals extract (28%) and placebo (26%). Total and partial Mayo scores favored —CBD-rich botanical extract ($p = 0.068$) and ($p = 0.038$) respectively. Subjective physician's global assessment of illness severity, subject's global impression of change, and patient-reported QoL outcomes. —improved for patients, CBD-rich botanical extract ($p = 0.069$), ($p = 0.003$), ($p = 0.065$), respectively. —CRP measured but not reported.
Low-dose CBD extract Established moderate active CD (20) [33]	PRCT parallel allocation	Oral administration as an oil —5 mg/Kg weight —8 weeks	—CBD was safe; however had no beneficial effects on moderately Active CD was observed. —CDAI no difference between groups ($p > 0.05$) —CRP ($p > 0.05$) between groups.
THC-rich cannabis extract Patients with active CD (21) [35]	Smoking	Inhaled | smoking —administration content 0.5 g of dried cannabis flowers corresponding to 115 mg THC. —8 weeks	—1° endpoint, induction of remission (CDAI score <150) achieved by 45% cannabis group versus 10% placebo group ($p > 0.05$). —Complete remission (CDAI score <150) achieved by 5 of 11 cannabis group versus 1 of 10 placebo group ($p > 0.05$). —CRP ($p > 0.05$). No induction of remission —CRP ($p > 0.05$) between groups.
Source Dry processed plant (13) [36]	Pilot study, single arm —Inhaled cannabis UC | CD | colonic IBD	Inhaled cannabis —dose of 50 g dry processed plant per month —12 weeks	↑ general health perception ($p = 0.001$) ↑ social functioning ($p = 0.0002$) ↑ ability to work ($p = 0.0005$) ↓ physical pain ($p = 0.004$) ↓ depression ($p = 0.007$) Schematic scale of health perception showed ↑ score from 4.1 ± 1.43 to 7 ± 1.42 ($p = 0.0002$) —CRP ($p > 0.05$) between groups.

THC, Δ9-tetrahydrocannabinol; CBD, Cannabidiol; UC, ulcerative colitis; CD, Crohn's disease; DBPCRCT, double blind placebo controlled randomized clinical trial; PRCT, placebo randomized controlled study; PEA, palmitoylethanolamide; AEA, arachidonoylethanolamine; 2-AG, 2-arachidonoylglycerol; LDAI, Lichtiger Disease Activity Index; CDAI, The Crohn's disease Activity Index; AA, arachidonic acid; OEA, oleoylethanolamide; IBD, inflammatory bowel disease; QoL, quality of life; CBG, cannabigerol; CBC, Cannabichromene; CBDV, Cannabidivarin; CRP, C-Reactive Protein; eCBs, endocannabinoids. ↑, increase; ↓, decrease.

A recent observational cohort study from Canada [39] reported on the use of cannabis to manage IBD symptomatology, both in UC and CD. The observational study included 254 participants diagnosed with IBD (i.e., 148 with CD, 90 with UC, and 16 with indeterminate colitis). The patients agreed to complete an online 40-question survey that included personal demographics, the history of their IBD disease, cannabis use, and the SIBDQ [39]. Recent cannabis use was reported by 41% of CD and 31% of UC participants. The authors concluded that the use of cannabis was associated with worse abdominal symptoms and QoL. Furthermore, clinicians were advised to first control IBD symptoms with evidence-based therapies and subsequently inquire about cannabis use with the aim of optimizing symptom management.

There is an intrinsic complexity that exists with the interactions between the gut microbiota and medicinal cannabis, which may limit the efficacy of THC and CBD to favourably influence anti-inflammatory responses in the gut. As we have previously noted here, cannabis molecules interact with G-protein-coupled receptors (GPCRs), particularly the CB_1 and CB_2 [17]. Recently, it has been reported that the intestinal microbiota may mediate pharmaceutical drug metabolism, affecting pharmacological efficacy [40]. Wu and colleagues [40] reported the broad impact that human gut commensal bacteria on GPCR-targeted drug structures and actions through diverse intestinal microbiota-mediated biotransformation. Similarly, the gut microbiota can play a crucial role in the metabolism of endogenous cannabinoids, affecting bioavailability and pharmacological activity. Several studies have identified microbial enzymes capable of metabolizing cannabinoids, leading to the formation of active or inactive metabolites [10,41–43].

It stands to reason that metabolic activities from the human intestinal microbiota may significantly affect the efficacy of THC and CBD. It is known that gut bacteria can metabolize cannabis molecules. A murine model report showed that intestinal commensal bacteria metabolized THC into 11-hydroxy-THC (11-OH-THC), exhibiting a greater potency than THC [44]. Whereas 11-nor-9-carboxy-THC (THC-COOH) is an inactive form of THC. In addition, CBD can be metabolized into 7-hydroxy-CBD, a compound that has been reported from *in vitro* studies to have potential anti-inflammatory properties [45]. Preclinical and specific clinical studies have shown that cannabinoids can reduce inflammation in rodent models of colitis [10]. An additional laboratory animal study showed that THC administered to adolescent and mature rats exacerbated chemically induced IBD in that murine model [46].

Notwithstanding, clinical evidence from human studies has been limited and centred on surveys and small trials (Table 1). While clinical studies with lower numbers of participants have shown that cannabis can improve QoL and improve symptoms such as diarrhea and abdominal pain, there was no significant reduction in inflammatory markers [47]. This view has been further emphasized by a recent scoping review that suggested that patients who use cannabis for IBD are a cohort with refractory disease and lower QoL who go on to report improvements in IBD symptom management [38]. The idea that medicinal cannabis molecules (e.g., THC + CBD or CBD alone) could reduce the underlying IBD activity was posited to be very modest, warranting further studies. The clinical studies with patients diagnosed with IBD treated with THC and or CBD (Table 1) that assessed the effect on inflammation in a systemic inflammatory marker (i.e., blood CRP) resulted in no improvement in inflammation with the administration of medicinal cannabis formulations [32–36].

Intestinal Dysbiosis Affects Drug Efficacy in IBD

Gut commensal bacteria's metabolic activities involve the fermentation of complex carbohydrates to produce short-chain fatty acids (SCFAs) [48], the synthesis of amino acids [48], and the synthesis of vitamins (e.g., biotin and phylloquinone) [49]. The intestinal microbiota also participates in the development and function of both local and systemic hematological structures [50,51]. Importantly, the uncompromised gut microbiota has been reported to protect against pathobiont infections through colonization resistance [52]. A stable gut microbiome and microbiota are reported to designate a healthy gut profile deemed as a steady state, with the multiplicity of microorganisms, consisting of bacteria, enteric viruses, and fungi [53–55].

Intestinal dysbiosis is often defined as an imbalance in the gut of the resident community of bacterial microorganisms that cohabitate the intestines. Relevant to IBD, the lack of variety and balance in the intestinal microbiota (i.e., refers to bacterial species in the gut) results in a dysbiotic unbalanced overview of the gut resident bacteria that is causally a major contributor to progressing pathological diseases such as IBD [56]. An imbalanced gut microbiota can significantly influence drug efficacy (as well as medicinal cannabis efficacy) by varying drug absorption, metabolism, and the overall response by the host, factors that potentially lead to reduced therapeutic outcomes or increased toxicity [57].

The intestines are continually exposed to external perturbations such as infections, antibiotics, and dietary changes. The gut ecosystem, though, has an inherent resilience capacity to respond to such adverse events, thereby maintaining the local equilibrium tone [58]. By contrast, though gut dysbiosis can also be a resilient outcome that can increase the risk of inflammatory diseases such as IBD [58]. When a detrimental disturbance in the complex biological system of the microbiome and more specifically the microbiota occurs, a dysbiotic state ensues that increases the risk of maintaining an inflammatory state in the gut [58], as so happens with IBD conditions. Altering the state of the

intestinal microbiota can lead a long-term, lasting compositional and functional changes in the bacterial communities in the intestines of the host [56,58].

It is scientifically accepted that the ECS interacts with the intestinal commensal cohort of bacteria. Inflammatory conditions such as IBD have been linked with aberrations of the gut microbiota [56]. UC and CD comprise the two main types of IBD, termed as chronic, resulting in relapsing and remitting inflammation of the intestines [56]. Patients diagnosed with IBD can be either in an active phase of the disease or in remission. Remission is characterized by a decrease or lack of symptoms, together with the absence of biochemical, endoscopic, or radiological inflammatory clinical evidence. Irrespective, clinical studies that administered medicinal cannabis to treat inflammation did not demonstrate efficacy, exemplified by failure to reduce CRP blood marker (Table 1).

The deviations in the complexity and conformity of intestinal bacterial communities have been described for UC [59,60] and CD [59]. Mechanistic studies on the abundance of anaerobic bacterial species in the gut reported as reduced in concentration cite those bacterial species that elaborate SCFAs (e.g., acetate, butyrate) [37]. Including species *Roseburia hominis* and *Faecalibacterium prausnitzii* [61], associated with progressing a proinflammatory metabolic state. Proinflammatory metabolism in the gut is detrimental to the intestinal mucosa [62]. A study that compared UC and CD patients with those without IBD has found that the profile of gut bacteria showed significant increases in *Proteobacteria* and significant decreases in *Firmicutes* and *Bacteroidetes* [62]. Interestingly, there were significant observed differences in gut bacterial genera between CD and UC diagnosed patients [62]. Significant increases were observed in *Escherichia*, *Ruminococcus (R. gnavus)*, *Cetobacterium*, *Actinobacillus*, and *Peptostreptococcus* genera in patients diagnosed with CD, and significant increases in *Faecalibacterium*, *Coprococcus*, *Prevotella*, and *Roseburia* genera in patients diagnosed with UC [62].

Further disruptions of the eubiosis tone of the intestines have been observed in IBD, with amino acid biosynthesis [63–65] and carbohydrate metabolism [63] reported to be decreased in favour of nutrient uptake by the microbiota. Clusters and various species of intestinal bacteria have been reported to be differentially abundant between controls and patients with IBD in remission [66–68]. This indicates that intestinal dysbiosis may persist despite patients being in remission, mechanistically contributing to the chronicity of IBD.

Orally administered medicinal cannabis has been suggested to shift the abundance of intestinal bacteria [10]. The direction of the shift is contentious, depending on the study. Laboratory animal studies have shown that cannabis administration can alter the abundance of specific bacterial taxa in the intestines following cannabis exposure [69]. Chronic THC administration in mice led to changes in the gut microbiota, with an increase in the relative abundance of *Akkermansia muciniphila*, a bacterium associated with improved gut barrier function and metabolic health [70]. Conversely, cannabis use in humans was linked to an increased abundance of *Bacteroides* species in the human gut microbiota, which might be associated with gut inflammation and metabolic disorders [71]. Such effects may lead to an intensifying effect in IBD, which is also subject to intestinal dysbiosis. These antagonistic results are further complicated by obesity in IBD. Obesity has been associated with gut dysbiosis [72]. Additionally, obesity has been increasingly reported to be prevalent in individuals with IBD, suggesting that it may negatively impact disease outcomes, potentially increasing the risk of complications (e.g., type 2 diabetes) and reducing the effectiveness of some treatments [73]. Given that the relationship between obesity and medicinal cannabis use is complex, oral administration of cannabis products to influence IBD inflammation may be contraindicated in chronic cannabis users with the increased risk of augmenting visceral fat [74]. Furthermore, a recent national Dutch registry study concluded that obesity correlated with lower odds of steroid-free clinical remission in patients diagnosed with IBD at 24 weeks after the initiation of treatment [75].

Vermiform Appendix Microbiota Dysbiosis Tolerates IBD

The vermiform appendix continues to be implicated in the pathogenesis and clinical course of UC [76]. Research data strongly posits that an inflamed appendix could exacerbate IBD, principally UC. In a Danish cohort study of 7,132,317 individuals over a 14-year period, the study investigated the impact of a family history of appendicitis as to whether there was a protective effect against UC development, afforded by surgical removal of the appendix [77]. The study reported that a personal history of appendicitis and surgical removal of the appendix at age less than 20 years, and a first-degree relative with appendicitis at age less than 20 years without a personal history of appendicitis, were significantly associated with a lower risk of UC.

The clinical evidence, though, remains contentious. Ko *et al*. [78] in an Australian study reported that appendectomy was a risk factor for UC among Middle Eastern migrants, while it was a protective factor among Caucasian populations in Australia. In addition, investigators have reported an inconsistent therapeutic effect on treating UC patients who were resistant to conventional medical therapy with appendectomy [79,80]. There is therefore a requirement to investigate whether appendiceal orifice inflammation is a contributing factor to the development of UC [79]. Concordant with this view is that presented from a recent systematic review [81] that concluded that a previous appendectomy reduces the risk of future colectomy.

Further complicating the clinical picture, Welsh and colleagues [81] (2022) review substantiated that therapeutic appendectomy may have a potential role in refractory left-sided UC. These patients have been reported to present with low QoL issues [82]. The surgical removal of the appendix in patients with refractory UC resulted in pathological improvement in colonic inflammation with complete endoscopic remission after 1 year post-surgery [83]. These results indicate a strong correlation with QoL and a decreased incidence of UC, and with reduced severity of inflammation [76]. The overall data influences and confirms that appendicitis has a relationship with UC [76,84]. Observational studies [83,85,86] seem to confirm this impression, positing that the appendix may have a role in the pathogenesis of UC, yet the nature of the association remains unclear [87].

What has been postulated over time is that local appendiceal bacterial dysbiosis may be the trigger for developing or tolerating UC [88]. Notwithstanding, numerous observational studies have reported the negative influence that the status of the surgical removal of the vermiform appendix in humans may have, with an adverse association with IBD disease states, not only with UC [89–93] but also with CD [89,90,94]. Research suggests that there is a link between intestinal microbiome dysbiosis and appendicitis [95]. This indicates that there is an imbalance in the gut cohort of bacteria, highlighting a decrease in the abundance of beneficial commensal bacteria with a concomitant increase in the abundance of pathobionts that may contribute to the development and progression of appendicitis [95]. Aberrant changes in the flux of the microbiota in the gut are consistent with the idea that intestinal dysbiosis is present in the colon and in the appendix, which supports the progression of IBD.

Recently, an appendix with a dysbiotic microbiota strongly suggested that appendicitis may be linked to intestinal microbial dysbiosis [96]. Signifying that an imbalance in the gut microbiota composition and diversity contributed to inflammation and the development of the disease [96]. Furthermore, at the genus level, Lee and colleagues [96] (2022) reported an increased abundance of potential pathogens such as *Parvimonas* and *Acinetobacter*, and a decrease in commensal taxa such as *Faecalibacterium*, *Blautia,* and *Lachnospiraceae* in appendicitis patients compared to healthy controls.

Mechanistically, studies support the notion that appendectomy can reduce UC severity by preventing appendiceal immune stimulation of the intestine, possibly via secretion of pro-inflammatory cytokines from the appendix and recolonization of abnormal/pathobiont bacteria in the colon from the appendix reservoir [76]. Evidence in support of this idea comes from a population-based study conducted in Sweden, in which childhood appendicitis was associated with protection against UC, whether it was treated with appendectomy or medically [97]. However, data on medically managed appendicitis are limited owing to the primary surgical management of appendicitis. The tone of the ECS can be disrupted by intestinal dysbiosis [98]. This, combined with an appendix harbouring a dysbiotic microbiota that contributes to colonic dysbiosis in ulcerative colitis, may make it clinically challenging to achieve and sustain remission of the underlying inflammatory condition with medicinal cannabis.

Discussion

The intestinal tract comprises a structure that is approximately 9–10 meters in length from the oral cavity to the anus [99]. The distinctive and abundant bacterial species that inhabit the gut present a complement of genes that significantly outnumber the human host's genes [100]. Moreover, the bacterial species that inhabit the intestines collectively exemplify an array of genes that enable critical functions that contribute to the host's health [100]. Consequently, human hosts encounter in the intestines several distinct bacterial communities that elaborate important metabolic activities [48]. This IBD scoping review presents a complex disease that has an accepted consideration of both a genetic predisposition and gut dysbiosis (i.e., an imbalance in the intestinal microbiome) [101]. Genetic variations can significantly influence the composition and function of the intestinal microbiota, and gut dysbiosis can trigger or worsen IBD [101]. Especially with observations that reduced levels of acetate-to-butyrate converting bacteria, such as those from the *Roseburia spp*, have been reported in patients diagnosed with IBD.

Marijuana that has been cultivated from the flowering plant that is *Cannabis sativa* Linn. is often used for symptom control in patients with IBD [102]. Medicinal cannabis is reported to improve the level of lifestyle stressors, improve sleeping patterns, and intestinal symptoms such as abdominal pain, diarrhea, and reduced appetite [102,103]. Yet specific indicators from clinical studies that report on improving inflammation in IBD have not provided useful clinical insights. Several clinical studies with small participant numbers [30–36] have investigated blood levels of CRP, questionnaires (e.g., QoL) inflammatory disease indices (e.g., LDAI, CDAI), reporting inconsistent results. The objective inflammatory marker CRP did not show any improvement with the use of medicinal cannabis either as a single or as a mixture of cannabinoid molecules (e.g., CBD or THC). The improvement in scores reported from questionnaires and disease indices should be interpreted with caution due to the placebo effect.

While a few small clinical studies have not demonstrated improvement in a clinical inflammatory marker for the underlying disease of IBD (e.g., C-Reactive Protein), a recent Canadian study concluded that the use of cannabis was associated with worse abdominal symptoms and QoL. A worse disease prognosis has been previously supported by others [7,104]. In concert with our scoping review

here, a meta-analysis [7] that described the clinical outcomes from 5 randomized clinical studies and 15 non-randomized studies that investigated the use of cannabis to manage IBD symptoms reported that there may be some benefit from patient-reported outcomes, without improvement in the fundamental intestinal inflammation of the disease. Given the clinical history of IBD linked to a dysbiotic gut profile, the natural and quick fix offered by the administration of medicinal cannabis products for the underlying inflammation of the disease may not be indicated for all patients.

Intestinal dysbiosis has been strongly posited to be central to progressing the disease [105]. Personal lifestyle and environmental factors that have been deemed stressors can adversely affect the course of IBD [105]. The ECS, a multi-signalling system in the intestines, is believed to play a significant role in regulating the stress response, which can be strongly impacted by both acute and chronic stress. Consequently, stress can alter the levels of endocannabinoids, arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), affecting the expression and sensitivity of cannabinoid receptors CB_1 and CB_2, which can then lead to the dysregulation of the ECS. Dysregulation of the ECS can potentially contribute to maintaining IBD. The administration of medicinal cannabis may then be ineffective in improving the underlying IBD disease.

Additional treatment modalities for IBD can involve probiotics, prebiotics, fecal microbiota transplantations (FMT), as well as nutritional interventions [106–108]. Clinical evidence shows that probiotics have a favourable efficacy and safety profile in the treatment and improvement of gut disorders [106,109]. The administration of probiotics, particularly multi-strain formulations, has been reported as efficacious for the induction of clinical remission and the prevention of relapse in UC patients as well as for relapsing pouchitis [109], while for efficacy in CD, the clinical evidence is contentious [106,109]. In addition, it has been reported that FMT may increase the proportion of people with active UC who achieve clinical and endoscopic remission [107]. However, the evidence regarding serious adverse events and the ability of FMT to induce and maintain remission in patients diagnosed with UC remains contentious. The variability in reported results has led to inconclusive findings about its long-term clinical therapeutic benefits.

Conclusion

In small clinical studies, the administration of inhaled or oral medicinal cannabis products has not achieved modulation of the underlying condition of inflammation in IBD, whether it be for UC or CD. What has been reported is an important improvement in the QoL of patients diagnosed with IBD. Improvements in QoL were suggested for those patients diagnosed with refractory IBD (e.g., UC) who had been prescribed medicinal cannabis. These patients often present with low levels of QoL, as medicinal cannabis may provide a beneficial outcome. Improvement in lifestyle issues such as mental states with the adoption of mind body medicine modalities (e.g., meditation) with nutrition, the adoption of functional foods (e.g., prebiotics) and physical activity (e.g., yoga) comprise interventions that could work in concert with prescriptions for medicinal cannabis to treat IBD and a dysbiotic gut microbiota.

Availability of Data and Materials

Not applicable.

Author Contributions

LV, DO and MT were involved in the conceptualization, drafting and critical revision of the final manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest with the contents of the current manuscript. LV has investigated, participated in clinical studies, and published manuscripts on medicinal cannabis. DO has co-authored manuscripts on medicinal cannabis and is an employee of Health House, a distributor of medicinal cannabis. MT has co-authored manuscripts on medicinal cannabis and has no other conflict of interest. Fig. 1 was created using BioRender. The authors have no financial or personal relationship with BioRender, and the use of this tool does not imply any endorsement.

References

[1] Hracs L, Windsor JW, Gorospe J, Cummings M, Coward S, Buie MJ, *et al*. Global evolution of inflammatory bowel disease across epidemiologic stages. Nature. 2025; 642: 458–466. https://doi.org/10.1038/s41586-025-08940-0.

[2] Kaplan GG. The global burden of IBD: from 2015 to 2025. Nature Reviews. Gastroenterology & Hepatology. 2015; 12: 720–727. https://doi.org/10.1038/nrgastro.2015.150.

[3] Sonnenburg ED, Sonnenburg JL. The ancestral and industrialized gut microbiota and implications for human health. Nature Reviews. Microbiology. 2019; 17: 383–390. https://doi.org/10.1038/s41579-019-0191-8.

[4] Cui G, Liu H, Xu G, Laugsand JB, Pang Z. Exploring Links Between Industrialization, Urbanization, and Chinese Inflammatory Bowel Disease. Frontiers in Medicine. 2021; 8: 757025. https://doi.org/10.3389/fmed.2021.757025.

[5] Tavakoli P, Vollmer-Conna U, Hadzi-Pavlovic D, Grimm MC. A Review of Inflammatory Bowel Disease: A Model of Microbial, Immune and Neuropsychological Integration. Public Health Reviews. 2021; 42: 1603990. https://doi.org/10.3389/phrs.2021.1603990.

[6] Yau CE, Lim GSJ, Ang AYH, Lim YL, Goh OQM, Siah KTH, *et al*. Examining the Association Between Overweight, Obesity, and Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. Nutrients. 2024; 16: 3984. https://doi.org/10.3390/nu16233984.

[7] Doeve BH, van de Meeberg MM, van Schaik FDM, Fidder HH. A Systematic Review With Meta-Analysis of the Efficacy of Cannabis and Cannabinoids for Inflammatory Bowel Disease: What Can We Learn From Randomized and Nonrandomized Studies? Journal of Clinical Gastroenterology. 2021; 55: 798–809. https://doi.org/10.1097/MCG.0000000000001393.

[8] Wu Y, Jiang Z, Su Ri GG, Wang L, Tian F, Liu L. Meta-analysis of the effectiveness of combined enteral nutrition therapy for inflammatory bowel disease. Medicine. 2024; 103: e40499. https://doi.org/10.1097/MD.0000000000040499.

[9] Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nature Medicine. 2016; 22: 1079–1089. https://doi.org/10.1038/nm.4185.

[10] Al-Khazaleh AK, Jaye K, Chang D, Münch GW, Bhuyan DJ. Buds and Bugs: A Fascinating Tale of Gut Microbiota and Cannabis in the Fight against Cancer. International Journal of Molecular Sciences. 2024; 25: 872. https://doi.org/10.3390/ijms25020872.

[11] Gupta A, Erridge S, Graf V, Kelada M, Bapir L, Jesuraj N, *et al*. UK medical cannabis registry: an updated analysis of clinical outcomes of cannabis-based medicinal products for inflammatory bowel disease. Expert Review of Gastroenterology & Hepatology. 2024; 18: 829–838. https://doi.org/10.1080/17474124.2024.2443574.

[12] Cohen L, Neuman MG. Cannabis and the Gastrointestinal Tract. Journal of Pharmacy & Pharmaceutical Sciences: a Publication of the Canadian Society for Pharmaceutical Sciences, Societe Canadienne des Sciences Pharmaceutiques. 2020; 23: 301–313. https://doi.org/10.18433/jpps31242.

[13] Pandey S, Kashif S, Youssef M, Sarwal S, Zraik H, Singh R, *et al*. Endocannabinoid system in irritable bowel syndrome and cannabis as a therapy. Complementary Therapies in Medicine. 2020; 48: 102242. https://doi.org/10.1016/j.ctim.2019.102242.

[14] Navarrete F, García-Gutiérrez MS, Jurado-Barba R, Rubio G, Gasparyan A, Austrich-Olivares A, *et al*. Endocannabinoid System Components as Potential Biomarkers in Psychiatry. Frontiers in Psychiatry. 2020; 11: 315. https://doi.org/10.3389/fpsyt.2020.00315.

[15] Wang Y, Guo J, Mao Z, Chen Y. Symphony of the gut microbiota and endocannabinoidome: a molecular and functional perspective. Frontiers in Cellular and Infection Microbiology. 2025; 15: 1566290. https://doi.org/10.3389/fcimb.2025.1566290.

[16] Schiano Moriello A, Di Marzo V, Petrosino S. Mutual Links between the Endocannabinoidome and the Gut Microbiome, with Special Reference to Companion Animals: A Nutritional Viewpoint. Animals: an Open Access Journal from MDPI. 2022; 12: 348. https://doi.org/10.3390/ani12030348.

[17] Vitetta L, Nation T, Oldfield D, Thomsen M. Medicinal Cannabis and the Intestinal Microbiome. Pharmaceuticals (Basel, Switzerland). 2024; 17: 1702. https://doi.org/10.3390/ph17121702.

[18] Charitos IA, Inchingolo AM, Ferrante L, Inchingolo F, Inchingolo AD, Castellaneta F, *et al*. The Gut Microbiota's Role in Neurological, Psychiatric, and Neurodevelopmental Disorders. Nutrients. 2024; 16: 4404. https://doi.org/10.3390/nu16244404.

[19] Srivastava RK, Lutz B, Ruiz de Azua I. The Microbiome and Gut Endocannabinoid System in the Regulation of Stress Responses and Metabolism. Frontiers in Cellular Neuroscience. 2022; 16: 867267. https://doi.org/10.3389/fncel.2022.867267.

[20] Hryhorowicz S, Kaczmarek-Ryś M, Zielińska A, Scott RJ, Słomski R, Pławski A. Endocannabinoid System as a Promising Therapeutic Target in Inflammatory Bowel Disease - A Systematic Review. Frontiers in Immunology. 2021; 12: 790803. https://doi.org/10.3389/fimmu.2021.790803.

[21] Karhson DS, Hardan AY, Parker KJ. Endocannabinoid signaling in social functioning: an RDoC perspective. Translational Psychiatry. 2016; 6: e905. https://doi.org/10.1038/tp.2016.169.

[22] Sera L, Hempel-Sanderoff C. Cannabis Science and Therapeutics: An Overview for Clinicians. Journal of Clinical Pharmacology. 2024; 64: 499–513. https://doi.org/10.1002/jcph.2400.

[23] Sagar KA, Gruber SA. The Complex Relationship Between Cannabis Use and Mental Health: Considering the Influence of Cannabis Use Patterns and Individual Factors. CNS Drugs. 2025; 39: 113–125. https://doi.org/10.1007/s40263-024-01148-2.

[24] Ong IM, Gonzalez JG, McIlwain SJ, Sawin EA, Schoen AJ, Adluru N, *et al*. Gut microbiome populations are associated with structure-specific changes in white matter architecture. Translational Psychiatry. 2018; 8: 6. https://doi.org/10.1038/s41398-017-0022-5.

[25] McCartney D, Arkell TR, Irwin C, McGregor IS. Determining the magnitude and duration of acute Δ^9-tetrahydrocannabinol (Δ^9-THC)-induced driving and cognitive impairment: A systematic and meta-analytic review. Neuroscience and Biobehavioral Reviews. 2021; 126: 175–193. https://doi.org/10.1016/j.neubiorev.2021.01.003.

[26] Jacobson MR, Watts JJ, Boileau I, Tong J, Mizrahi R. A systematic review of phytocannabinoid exposure on the endocannabinoid system: Implications for psychosis. European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology. 2019; 29: 330–348. https://doi.org/10.1016/j.euroneuro.2018.12.014.

[27] D'Souza DC, Cortes-Briones JA, Ranganathan M, Thurnauer H, Creatura G, Surti T, *et al*. Rapid Changes in Cannabinoid 1 Receptor Availability in Cannabis-Dependent Male Subjects After Abstinence From Cannabis. Biological Psychiatry. Cognitive Neuroscience and Neuroimaging. 2016; 1: 60–67. https://doi.org/10.1016/j.bpsc.2015.09.008.

[28] Osman M, Papon N, Weill FX. Endocannabinoids Attenuate the Virulence of Certain Enteropathogenic Bacteria. Trends in Microbiology. 2021; 29: 185–187. https://doi.org/10.1016/j.tim.2020.12.008.

[29] Ellermann M, Pacheco AR, Jimenez AG, Russell RM, Cuesta S, Kumar A, *et al*. Endocannabinoids Inhibit the Induction of Virulence in Enteric Pathogens. Cell. 2020; 183: 650–665.e15. https://doi.org/10.1016/j.cell.2020.09.022.

[30] Tartakover Matalon S, Azar S, Meiri D, Hadar R, Nemirovski A, Abu Jabal N, *et al*. Endocannabinoid Levels in Ulcerative Colitis Patients Correlate With Clinical Parameters and Are Affected by Cannabis Consumption. Frontiers in Endocrinology. 2021; 12: 685289. https://doi.org/10.3389/fendo.2021.685289.

[31] Irving PM, Iqbal T, Nwokolo C, Subramanian S, Bloom S, Prasad N, *et al*. A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich

Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis. Inflammatory Bowel Diseases. 2018; 24: 714–724. https://doi.org/10.1093/ibd/izy002.

[32] Naftali T, Bar-Lev Schleider L, Almog S, Meiri D, Konikoff FM. Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial. Journal of Crohn's & Colitis. 2021; 15: 1799–1806. https://doi.org/10.1093/ecco-jcc/jjab069.

[33] Naftali T, Mechulam R, Marii A, Gabay G, Stein A, Bronshtain M, *et al*. Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial. Digestive Diseases and Sciences. 2017; 62: 1615–1620. https://doi.org/10.1007/s10620-017-4540-z.

[34] Naftali T, Bar-Lev Schleider L, Scklerovsky Benjaminov F, Konikoff FM, Matalon ST, Ringel Y. Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial. PloS One. 2021; 16: e0246871. https://doi.org/10.1371/journal.pone.0246871.

[35] Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clinical Gastroenterology and Hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association. 2013; 11: 1276–1280.e1. https://doi.org/10.1016/j.cgh.2013.04.034.

[36] Lahat A, Lang A, Ben-Horin S. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. Digestion. 2012; 85: 1–8. https://doi.org/10.1159/000332079.

[37] Takahashi K, Nishida A, Fujimoto T, Fujii M, Shioya M, Imaeda H, *et al*. Reduced Abundance of Butyrate-Producing Bacteria Species in the Fecal Microbial Community in Crohn's Disease. Digestion. 2016; 93: 59–65. https://doi.org/10.1159/000441768.

[38] Brodaric A, Polikarpova A, Hong J. Cannabinoids for Inflammatory Bowel Disease: A Scoping Review. Cannabis and Cannabinoid Research. 2025; 10: 18–27. https://doi.org/10.1089/can.2024.0061.

[39] Iablokov V, Gregor J, Chande N, Ponich T, Jairath V, Khanna R, *et al*. Cannabis Use in Patients With Inflammatory Bowel Disease Following Legalization of Cannabis in Canada. Crohn's & Colitis 360. 2024; 6: otae031. https://doi.org/10.1093/crocol/otae031.

[40] Wu Q, Song D, Zhao Y, Verdegaal AA, Turocy T, Duncan-Lowey B, *et al*. Activity of GPCR-targeted drugs influenced by human gut microbiota metabolism. Nature Chemistry. 2025; 17: 808–821. https://doi.org/10.1038/s41557-025-01789-w.

[41] Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metabolism Reviews. 2014; 46: 86–95. https://doi.org/10.3109/03602532.2013.849268.

[42] Bansal S, Zamarripa CA, Spindle TR, Weerts EM, Thummel KE, Vandrey R, *et al*. Evaluation of Cytochrome P450-Mediated Cannabinoid-Drug Interactions in Healthy Adult Participants. Clinical Pharmacology and Therapeutics. 2023; 114: 693–703. https://doi.org/10.1002/cpt.2973.

[43] Balhara A, Tsang YP, Unadkat JD. Cannabidiol and Δ9-tetrahydrocannabinol induce drug-metabolizing enzymes, but not transporters, in human hepatocytes: Implications for predicting complex cannabinoid-drug interactions. Drug Metabolism and Disposition: the Biological Fate of Chemicals. 2025; 53: 100037. https://doi.org/10.1016/j.dmd.2025.100037.

[44] Watanabe K, Itokawa Y, Yamaori S, Funahashi T, Kimura T, Kaji T, *et al*. Conversion of cannabidiol to Δ9-tetrahydrocannabinol and related cannabinoids in artificial gastric juice, and their pharmacological effects in mice. Forensic Toxicology. 2007; 25: 16–21. https://doi.org/10.1007/s11419-007-0021-y.

[45] Borrelli F, Pagano E, Romano B, Panzera S, Maiello F, Coppola D, *et al*. Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychotropic cannabinoid. Carcinogenesis. 2014; 35: 2787–2797. https://doi.org/10.1093/carcin/bgu205.

[46] Dunford J, Lee AT, Morgan MM. Tetrahydrocannabinol (THC) Exacerbates Inflammatory Bowel Disease in Adolescent and Adult Female Rats. The Journal of Pain. 2021; 22: 1040–1047. https://doi.org/10.1016/j.jpain.2021.02.014.

[47] Kienzl M, Storr M, Schicho R. Cannabinoids and Opioids in the Treatment of Inflammatory Bowel Diseases. Clinical and Translational Gastroenterology. 2020; 11: e00120. https://doi.org/10.14309/ctg.0000000000000120.

[48] de Luca Silva B, Cendoroglo MS, Colleoni GWB. Gut Microbiota and Metabolic Biomarkers Associated With Longevity. Nutrition Reviews. 2025; nuaf027. https://doi.org/10.1093/nutrit/nuaf027.

[49] Alrubaye HS, Kohl KD. Abundance and Compositions of B-Vitamin-Producing Microbes in the Mammalian Gut Vary Based on Feeding Strategies. MSystems. 2021; e0031321. https://doi.org/10.1128/mSystems.00313-21.

[50] Atarashi K, Tanoue T, Ando M, Kamada N, Nagano Y, Narushima S, *et al*. Th17 Cell Induction by Adhesion of Microbes to Intestinal Epithelial Cells. Cell. 2015; 163: 367–380. https://doi.org/10.1016/j.cell.2015.08.058.

[51] Bouskra D, Brézillon C, Bérard M, Werts C, Varona R, Boneca IG, *et al*. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature. 2008; 456: 507–510. https://doi.org/10.1038/nature07450.

[52] Stecher B, Berry D, Loy A. Colonization resistance and microbial ecophysiology: using gnotobiotic mouse models and single-cell technology to explore the intestinal jungle. FEMS Microbiology Reviews. 2013; 37: 793–829. https://doi.org/10.1111/1574-6976.12024.

[53] Fassarella M, Blaak EE, Penders J, Nauta A, Smidt H, Zoetendal EG. Gut microbiome stability and resilience: elucidating the response to perturbations in order to modulate gut health. Gut. 2021; 70: 595–605. https://doi.org/10.1136/gutjnl-2020-321747.

[54] Chilloux J, Neves AL, Boulangé CL, Dumas ME. The microbial-mammalian metabolic axis: a critical symbiotic relationship. Current Opinion in Clinical Nutrition and Metabolic Care. 2016; 19: 250–256. https://doi.org/10.1097/MCO.0000000000000284.

[55] Parkar SG, Kalsbeek A, Cheeseman JF. Potential Role for the Gut Microbiota in Modulating Host Circadian Rhythms and Metabolic Health. Microorganisms. 2019; 7: 41. https://doi.org/10.3390/microorganisms7020041.

[56] Pisani A, Rausch P, Bang C, Ellul S, Tabone T, Marantidis Cordina C, *et al*. Dysbiosis in the Gut Microbiota in Patients with Inflammatory Bowel Disease during Remission. Microbiology Spectrum. 2022; 10: e0061622. https://doi.org/10.1128/spectrum.00616-22.

[57] Fan J, Jiang T, He D. Advances in the implications of the gut microbiota on the treatment efficacy of disease-modifying antirheumatic drugs in rheumatoid arthritis. Frontiers in Immunology. 2023; 14: 1189036. https://doi.org/10.3389/fimmu.2023.1189036.

[58] Sommer F, Anderson JM, Bharti R, Raes J, Rosenstiel P. The resilience of the intestinal microbiota influences health and disease. Nature Reviews. Microbiology. 2017; 15: 630–638. https://doi.org/10.1038/nrmicro.2017.58.

[59] Martinez C, Antolin M, Santos J, Torrejon A, Casellas F, Borruel N, *et al*. Unstable composition of the fecal microbiota in ulcer-

ative colitis during clinical remission. The American Journal of Gastroenterology. 2008; 103: 643–648. https://doi.org/10.1111/j.1572-0241.2007.01592.x.

[60] Rajilić-Stojanović M, Shanahan F, Guarner F, de Vos WM. Phylogenetic analysis of dysbiosis in ulcerative colitis during remission. Inflammatory Bowel Diseases. 2013; 19: 481–488. https://doi.org/10.1097/MIB.0b013e31827fec6d.

[61] Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, *et al*. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut. 2014; 63: 1275–1283. https://doi.org/10.1136/gutjnl-2013-304833.

[62] Nishino K, Nishida A, Inoue R, Kawada Y, Ohno M, Sakai S, *et al*. Analysis of endoscopic brush samples identified mucosa-associated dysbiosis in inflammatory bowel disease. Journal of Gastroenterology. 2018; 53: 95–106. https://doi.org/10.1007/s00535-017-1384-4.

[63] Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, *et al*. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biology. 2012; 13: R79. https://doi.org/10.1186/gb-2012-13-9-r79.

[64] Ma Y, Zhang Y, Xiang J, Xiang S, Zhao Y, Xiao M, *et al*. Metagenome Analysis of Intestinal Bacteria in Healthy People, Patients With Inflammatory Bowel Disease and Colorectal Cancer. Frontiers in Cellular and Infection Microbiology. 2021; 11: 599734. https://doi.org/10.3389/fcimb.2021.599734.

[65] Zheng X, Zhu Y, Zhao Z, Chu Y, Yang W. The role of amino acid metabolism in inflammatory bowel disease and other inflammatory diseases. Frontiers in Immunology. 2023; 14: 1284133. https://doi.org/10.3389/fimmu.2023.1284133.

[66] Wang W, Chen L, Zhou R, Wang X, Song L, Huang S, *et al*. Increased proportions of Bifidobacterium and the Lactobacillus group and loss of butyrate-producing bacteria in inflammatory bowel disease. Journal of Clinical Microbiology. 2014; 52: 398–406. https://doi.org/10.1128/JCM.01500-13.

[67] Lopez-Siles M, Enrich-Capó N, Aldeguer X, Sabat-Mir M, Duncan SH, Garcia-Gil LJ, *et al*. Alterations in the Abundance and Co-occurrence of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* in the Colonic Mucosa of Inflammatory Bowel Disease Subjects. Frontiers in Cellular and Infection Microbiology. 2018; 8: 281. https://doi.org/10.3389/fcimb.2018.00281.

[68] Cardoneanu A, Mihai C, Rezus E, Burlui A, Popa I, Cijevschi Prelipcean C. Gut microbiota changes in inflammatory bowel diseases and ankylosing spondilytis. Journal of Gastrointestinal and Liver Diseases: JGLD. 2021; 30: 46–54. https://doi.org/10.15403/jgld-2823.

[69] Al-Ghezi ZZ, Miranda K, Nagarkatti M, Nagarkatti PS. Combination of Cannabinoids, Δ9- Tetrahydrocannabinol and Cannabidiol, Ameliorates Experimental Multiple Sclerosis by Suppressing Neuroinflammation Through Regulation of miRNA-Mediated Signaling Pathways. Frontiers in Immunology. 2019; 10: 1921. https://doi.org/10.3389/fimmu.2019.01921.

[70] Cluny NL, Keenan CM, Duncan M, Fox A, Lutz B, Sharkey KA. Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (SAB378), a peripherally restricted cannabinoid CB1/CB2 receptor agonist, inhibits gastrointestinal motility but has no effect on experimental colitis in mice. The Journal of Pharmacology and Experimental Therapeutics. 2010; 334: 973–980. https://doi.org/10.1124/jpet.110.169946.

[71] Zhuang X, Xiong L, Li L, Li M, Chen M. Alterations of gut microbiota in patients with irritable bowel syndrome: A systematic review and meta-analysis. Journal of Gastroenterology and Hepatology. 2017; 32: 28–38. https://doi.org/10.1111/jgh.13471.

[72] Peña-Durán E, García-Galindo JJ, López-Murillo LD, Huerta-Huerta A, Balleza-Alejandri LR, Beltrán-Ramírez A, *et al*. Microbiota and Inflammatory Markers: A Review of Their Interplay, Clinical Implications, and Metabolic Disorders. International Journal of Molecular Sciences. 2025; 26: 1773. https://doi.org/10.3390/ijms26041773.

[73] Breton J, Galmiche M, Déchelotte P. Dysbiotic Gut Bacteria in Obesity: An Overview of the Metabolic Mechanisms and Therapeutic Perspectives of Next-Generation Probiotics. Microorganisms. 2022; 10: 452. https://doi.org/10.3390/microorganisms10020452.

[74] Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M, *et al*. Metabolic effects of chronic cannabis smoking. Diabetes Care. 2013; 36: 2415–2422. https://doi.org/10.2337/dc12-2303.

[75] Oomkens D, Mujagic Z, de Vries A, van der Meulen-de Jong A, Straatmijer T, Löwenberg M, *et al*. Obesity Is Associated with Inferior Clinical Treatment Outcomes in Inflammatory Bowel Disease: A Nationwide Dutch Registry Study. Digestive Diseases and Sciences. 2025; 10.1007/s10620–10.1007/s10620–025–09052–5. https://doi.org/10.1007/s10620-025-09052-5.

[76] Arjomand Fard N, Armstrong H, Perry T, Wine E. Appendix and Ulcerative Colitis: a Key to Explaining the Pathogenesis and Directing Novel Therapies? Inflammatory Bowel Diseases. 2023; 29: 151–160. https://doi.org/10.1093/ibd/izac106.

[77] Nyboe Andersen N, Gørtz S, Frisch M, Jess T. Reduced risk of UC in families affected by appendicitis: a Danish national cohort study. Gut. 2017; 66: 1398–1402. https://doi.org/10.1136/gutjnl-2015-311131.

[78] Ko Y, Kariyawasam V, Karnib M, Butcher R, Samuel D, Alrubaie A, *et al*. Inflammatory Bowel Disease Environmental Risk Factors: A Population-Based Case-Control Study of Middle Eastern Migration to Australia. Clinical Gastroenterology and Hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association. 2015; 13: 1453–63.e1. https://doi.org/10.1016/j.cgh.2015.02.045.

[79] Kuk KW, Gwon JY, Soh JS, Lim H, Kang HS, Moon SH, *et al*. Clinical significance and long-term prognosis of ulcerative colitis patients with appendiceal orifice inflammation. BMC Gastroenterology. 2022; 22: 532. https://doi.org/10.1186/s12876-022-02627-w.

[80] Park SH, Loftus EV, Jr, Yang SK. Appendiceal skip inflammation and ulcerative colitis. Digestive Diseases and Sciences. 2014; 59: 2050–2057. https://doi.org/10.1007/s10620-014-3129-z.

[81] Welsh S, Sam Z, Seenan JP, Nicholson GA. The Role of Appendicectomy in Ulcerative Colitis: Systematic Review and Meta-Analysis. Inflammatory Bowel Diseases. 2022; 28: e147–e148. https://doi.org/10.1093/ibd/izac191.

[82] Armuzzi A, Liguori G. Quality of life in patients with moderate to severe ulcerative colitis and the impact of treatment: A narrative review. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2021; 53: 803–808. https://doi.org/10.1016/j.dld.2021.03.002.

[83] Sahami S, Wildenberg ME, Koens L, Doherty G, Martin S, D'Haens GRAM, *et al*. Appendectomy for Therapy-Refractory Ulcerative Colitis Results in Pathological Improvement of Colonic Inflammation: Short-Term Results of the PASSION Study. Journal of Crohn's & Colitis. 2019; 13: 165–171. https://doi.org/10.1093/ecco-jcc/jjy127.

[84] Russel MG, Dorant E, Brummer RJ, van de Kruijs MA, Muris JW, Bergers JM, *et al*. Appendectomy and the risk of developing ulcerative colitis or Crohn's disease: results of a large case-control study. South Limburg Inflammatory Bowel Disease Study Group. Gastroenterology. 1997; 113: 377–382. https://doi.org/10.1053/gast.1997.v113.pm9247453.

[85] Koutroubakis IE, Vlachonikolis IG, Kapsoritakis A, Spanoudakis S, Roussomoustakaki M, Mouzas IA, *et al*. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: case-controlled study in Crete. Diseases of the Colon and Rectum. 1999; 42: 225–230. https://doi.org/10.1007/BF02237133.

[86] Naganuma M, Iizuka B, Torii A, Ogihara T, Kawamura Y, Ichinose M, *et al*. Appendectomy protects against the development of ulcerative colitis and reduces its recurrence: results of a multicenter case-controlled study in Japan. The American Journal of Gastroenterology. 2001; 96: 1123–1126. https://doi.org/10.1111/j.1572-0241.2001.03757.x.

[87] Agrawal M, Allin KH, Mehandru S, Faith J, Jess T, Colombel JF. The appendix and ulcerative colitis - an unsolved connection. Nature Reviews. Gastroenterology & Hepatology. 2023; 20: 615–624. https://doi.org/10.1038/s41575-023-00774-3.

[88] Roblin X, Neut C, Darfeuille-Michaud A, Colombel JF. Local appendiceal dysbiosis: the missing link between the appendix and ulcerative colitis? Gut. 2012; 61: 635–636. https://doi.org/10.1136/gutjnl-2011-300576.

[89] Chung WS, Chung S, Hsu CY, Lin CL. Risk of Inflammatory Bowel Disease Following Appendectomy in Adulthood. Frontiers in Medicine. 2021; 8: 661752. https://doi.org/10.3389/fmed.2021.661752.

[90] Radford-Smith GL, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG, *et al*. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. Gut. 2002; 51: 808–813. https://doi.org/10.1136/gut.51.6.808.

[91] Koutroubakis IE, Vlachonikolis IG, Kouroumalis EA. Role of appendicitis and appendectomy in the pathogenesis of ulcerative colitis: a critical review. Inflammatory Bowel Diseases. 2002; 8: 277–286. https://doi.org/10.1097/00054725-200207000-00007.

[92] Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. The New England Journal of Medicine. 2001; 344: 808–814. https://doi.org/10.1056/NEJM200103153441104.

[93] Cosnes J, Carbonnel F, Beaugerie L, Blain A, Reijasse D, Gendre JP. Effects of appendicectomy on the course of ulcerative colitis. Gut. 2002; 51: 803–807. https://doi.org/10.1136/gut.51.6.803.

[94] Kaplan GG, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. Gut. 2007; 56: 1387–1392. https://doi.org/10.1136/gut.2007.121467.

[95] Zhao L, Fang XD, Jia W, Bian ZX. Managing Chronic Diarrhea From a Gut Microbiota-Bile Acid Perspective. Clinical and Translational Gastroenterology. 2020; 11: e00208. https://doi.org/10.14309/ctg.0000000000000208.

[96] Lee MS, Sulit A, Frizelle F, Purcell R. The microbiome in adult acute appendicitis. Gut Microbiome (Cambridge, England). 2022; 3: e8. https://doi.org/10.1017/gmb.2022.7.

[97] Kiasat A, Ekström LD, Marsk R, Löf-Granström A, Gustafsson UO. Childhood appendicitis and future risk of inflammatory bowel disease - A nationwide cohort study in Sweden 1973-2017. Colorectal Disease: the Official Journal of the Association of Coloproctology of Great Britain and Ireland. 2022; 24: 975–983. https://doi.org/10.1111/codi.16128.

[98] Jansma J, Brinkman F, van Hemert S, El Aidy S. Targeting the endocannabinoid system with microbial interventions to improve gut integrity. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2021; 106: 110169. https://doi.org/10.1016/j.pnpbp.2020.110169.

[99] Hounnou G, Destrieux C, Desmé J, Bertrand P, Velut S. Anatomical study of the length of the human intestine. Surgical and Radiologic Anatomy: SRA. 2002; 24: 290–294. https://doi.org/10.1007/s00276-002-0057-y.

[100] Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. Nature Medicine. 2018; 24: 392–400. https://doi.org/10.1038/nm.4517.

[101] Imhann F, Vich Vila A, Bonder MJ, Fu J, Gevers D, Visschedijk MC, *et al*. Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. Gut. 2018; 67: 108–119. https://doi.org/10.1136/gutjnl-2016-312135.

[102] Ravikoff Allegretti J, Courtwright A, Lucci M, Korzenik JR, Levine J. Marijuana use patterns among patients with inflammatory bowel disease. Inflammatory Bowel Diseases. 2013; 19: 2809–2814. https://doi.org/10.1097/01.MIB.0000435851.94391.37.

[103] Kerlin AM, Long M, Kappelman M, Martin C, Sandler RS. Profiles of Patients Who Use Marijuana for Inflammatory Bowel Disease. Digestive Diseases and Sciences. 2018; 63: 1600–1604. https://doi.org/10.1007/s10620-018-5040-5.

[104] Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflammatory Bowel Diseases. 2014; 20: 472–480. https://doi.org/10.1097/01.MIB.0000440982.79036.d6.

[105] Farah A, Paul P, Khan AS, Sarkar A, Laws S, Chaari A. Targeting gut microbiota dysbiosis in inflammatory bowel disease: a systematic review of current evidence. Frontiers in Medicine. 2025; 12: 1435030. https://doi.org/10.3389/fmed.2025.1435030.

[106] Iheozor-Ejiofor Z, Kaur L, Gordon M, Baines PA, Sinopoulou V, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. The Cochrane Database of Systematic Reviews. 2020; 3: CD007443. https://doi.org/10.1002/14651858.CD007443.pub3.

[107] Imdad A, Pandit NG, Zaman M, Minkoff NZ, Tanner-Smith EE, Gomez-Duarte OG, *et al*. Fecal transplantation for treatment of inflammatory bowel disease. The Cochrane Database of Systematic Reviews. 2023; 4: CD012774. https://doi.org/10.1002/14651858.CD012774.pub3.

[108] Jaramillo AP, Abaza A, Sid Idris F, Anis H, Vahora I, Moparthi KP, *et al*. Diet as an Optional Treatment in Adults With Inflammatory Bowel Disease: A Systematic Review of the Literature. Cureus. 2023; 15: e42057. https://doi.org/10.7759/cureus.42057.

[109] Estevinho MM, Yuan Y, Rodríguez-Lago I, Sousa-Pimenta M, Dias CC, Barreiro-de Acosta M, *et al*. Efficacy and safety of probiotics in IBD: An overview of systematic reviews and updated meta-analysis of randomized controlled trials. United European Gastroenterology Journal. 2024; 12: 960–981. https://doi.org/10.1002/ueg2.12636.